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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,716	05/02/2001	Soren Nielsen	NIELSEN=3A	3819

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/845,716	NIELSEN ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,11 and 13-17* is/are pending in the application.

4a) Of the above claim(s) *11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5 and 13-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/1/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 02 December 2004 has been entered in full.

Applicants state that the listing of claims will replace all prior versions, and listings of claims in the application. Applicants state that claims 11-16, as presented September 24, 2001, have been renumbered 12-17, as there was already a claim 11 originally filed. Claims 3, 6-10 and 12 were cancelled.

The information disclosure statement filed 01 October 2001 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Applicants' election with traverse of Group I (claims 1-5, 11-13) and species election of heart (claim 2) and atheromatous disease with thrombosis (claim 14, old claim 13) 02 December 2003 is acknowledged.

The traversal is on the grounds that the Examiner has not clearly demarcated the allegedly distinct inventions and has failed to analyze the claims in the light of the criteria for distinctness. Applicants state that the Examiner could consider making a species restriction calling for election of a "patient population". Applicants argue that if the use of these two agents (alpha melanocyte stimulating hormone, MSH and erythropoietin, EPO) in tandem is not disclosed or suggested by the art, then the Examiner has no need to address specific diseases in her search. Applicants maintain that the Examiner appears ready to search conditions caused by ischemia of the tissue, condition caused by ischemia secondary to various conditions, where the ischemia is

due to septic shock or conditions associated with systemic hypotension. Applicants state that it is not a serious burden to search groups I-IV.

Applicants' arguments have been fully considered and are deemed partly persuasive. Because Applicant is free to claim their invention any way they choose, there will be situations wherein restriction within a Markush group is proper. The instant claims recite improper Markush groups because the diseases recited are not necessarily related. There is no generic feature that links the claims. Contrary to Applicants' assertion, ischemia is a broad term, which encompasses many diseases/conditions. While examination may possibly require a search of classes that overlap there is no reason to believe that the search would be co-extensive because a search is directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a search of relevant literature in many different areas of subject matter. Furthermore, a search of prior art may disclose references, which concern more than one species, however because many of the instant species are diverse from one another, a search of all of the species in one application would result in undue burden.

Applicants have elected the species heart and atheromatous disease with thrombosis (claims 2 and 14). Claims 15-17 are directed to patentably distinct species of the claimed invention. To further prosecution, the Examiner will elect a single disclosed species (first species recited) for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, 1

is generic. Diabetes mellitus (claim 15), conditions caused by surgery (claim 16) and ischemia due to septic shock (claim 17) will be examined.

Upon the allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should Applicant traverse on the ground that the species are not patentably distinct, Applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the Examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

The requirement is still deemed proper and is therefore made FINAL. Claims 1, 2, 4, 5, 13-17 are under examination. Applicant timely traversed the restriction (election) requirement 02 December 2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 5, 13-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for treating ischemia of the heart, comprising administering a pharmaceutically effective dose of alpha-MSH and EPO to the mammal in need thereof,

does not reasonably provide enablement for the following methods:

a method for treating any *condition in the tissue of the organ* of a mammal, said condition caused by ischemia of the tissue, comprising administering a pharmaceutically effective dose of alpha-MSH and EPO to the mammal in need thereof

a method of *preventing* a condition, *preventing* the establishment of the condition/symptom of the condition, *preventing* the progress of the condition/symptom of condition;

a method for treating or preventing a condition comprising administering *alpha-MSH equivalents and/or EPO equivalents.*

a method for treating or preventing *coronary artery disease, stenosis, atheromatous disease, diabetes mellitus, conditions caused by surgery of one or more organs* or *ischemia due to septic shock*.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or the invention commensurate in scope with these claims.

The instant specification teaches that ligation of the anterior intraventricular ramus from the left coronary artery (LCAL) in rats induce ischemia and eventually infarction in the anterior wall of the left ventricle of the heart. The infarction of the heart

is associated with the development of heart failure (page 38, lines 20-35). The specification teaches that alpha-MSH treatment significantly reduced the size of infarction. The reduction in infarction size was even more pronounced when alpha-MSH was given in combination with EPO (page 39, lines 3-17). The subject matter sought to be patented as defined by the claims is not supported by an enabling disclosure because of the following reasons.

Prevent means to completely stop a condition from occurring. "Prevention" is not a relative term, it is total. The specification is not enabled for a method of preventing or stopping any condition or disease. A very high degree of evidence is required, which is accepted in the art, that an absolute protection from the pathology exists over an extended period of time.

The specification fails to teach how to make and use alpha-MSH and EPO equivalents and provides no assay to evaluate the function of the equivalent. The specification states that alpha-MSH equivalent is preferably a substance acting on an alpha-MSH receptor (page 13, lines 9-14). The specification states that an EPO equivalent is preferably a substance acting on an EPO receptor (page 13, lines 19-22). Absent any means to assess the function of the equivalent, it would require an indeterminate quantity of fundamentally unpredictable investigational experimentation of the skilled artisan to determine whether any alpha-MSH or EPO equivalent could be used in the same manner as the native exemplar. Such experimentation would be undue for one skilled in this art. Furthermore, even were an assay provided, the specification would not support claims to alpha-MSH and EPO equivalents. The term

"equivalents" encompass sequence variants, mutants, chemicals, analogues, nucleic acid, lipids, macromolecules, etc. In order to make a sequence variant, for example, with the reasonable assurance that it would have the desirable properties of the invention, the artisan would need to know which regions of the disclosed polypeptide are responsible for the interactions underlying its biological function(s). As is well recognized in the art, any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter its functional properties. It is known for nucleic acids as well as proteins, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. The disclosure provides no guidance as to which regions of the protein would be tolerant of modification and which would not, and it provides no working example of any variant sequence which would be within the claims. It is in no way predictable that randomly selected mutations, deletions, *etc.* in the disclosed sequence would afford a protein having activity comparable to the one disclosed. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517).

Lastly, ligation of the anterior intraventricular ramus from the left coronary artery (LCAL) in a rat does not correlate to diabetes mellitus, conditions caused by surgery of

one or more organs and ischemia due to septic shock. Diabetes mellitus can encompass diabetes mellitus type I (juvenile), diabetes mellitus type II (adult onset) and diabetes mellitus, lipoatrophic. The specification would not enabled for this or *any condition* caused by surgery of one or more organs. Lastly, both the specification and Applicants fail to teach or recite literature which states that the rat model disclosed is *an art recognized model* for coronary artery disease, stenosis, diabetes mellitus, and atheromatous disease. The specification does not reveal working models for any of said conditions/diseases, which demonstrate successful treatment upon administration of alpha-MSH and EPO. While some of the recited diseases may share a common pathology of ischemia of tissue, there are many other elements, which characterize these conditions that are vastly different. The state of the prior art establishes various treatments for the diseases claimed in the instant application.

Due to the large quantity of experimentation necessary to completely stop a disease/condition/symptom from occurring, the large quantity of experimentation necessary to make, test and administer alpha-MSH and EPO equivalents compounds in a mammal and to treat diverse conditions/disease, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, and the breadth of the claims which fail to recite limitations regarding structural limitations for alpha-MSH and EPO equivalents, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 1, 2, 4, 5, 13-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification provides adequate written description for alpha-MSH and EPO but not alpha-MSH and EPO equivalents. The instant claims recite administering alpha-MSH and EPO equivalents.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

With the exception of alpha-MSH and EPO, the skilled artisan cannot envision the detailed chemical structure of the encompassed product, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. None of these sequences meet the written description provision of 35 USC 112, first paragraph. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only alpha-MSH and EPO, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Airaghi *et al.* American Heart Journal 130(2):204-11 (1995) in view of Wizemann *et al.*, Nephron 62(2):165-5 (1992). The instant claims are drawn to a method for treating or preventing a condition in the tissue of the organ(s) of a mammal, said condition caused by ischemia of the tissue, comprising administering a pharmaceutically effective dose of (1) alpha-MSH and/or an alph-MSH equivalent and (2) EPO and/or an EPO equivalent to the mammal in need thereof and a method according to claim 1 wherein the organ is selected from the group consisting of heart.

Airaghi *et al.* teach that patients with acute myocardial infarction (AMI) had plasma concentrations of alpha-MSH that were significantly greater than those in control subjects (page 207, 2nd paragraph and Figure 1). Airaghi *et al.* teach that alpha-MSH is released into circulation during myocardial ischemia and may reduce inflammation caused by cytokines. Airaghi *et al.* state that evidence from experimental models of acute myocardial infarction ischemia indicate that inflammation associated with ischemia and reperfusion contribute to tissue damage (page 208, 1st paragraph, Discussion). Airaghi *et al.* suggest that inflammatory mediators released during reperfusion can release alpha-MSH from cardiac cells and thereby reduce chemotaxis and inflammation (top of page 210). Airaghi *et al.* state that because inflammation caused by ischemia and reperfusion is an important component of myocardial infarction, the treatment of patients with AMI should include reduction of inflammation. Airaghi *et al.* propose that alpha-MSH, which has potent anti-cytokine properties associated with a

broad anti-inflammatory spectrum, would be useful in this condition (page 210, last paragraph).

Wizemann *et al.* teach that erythropoietin reduces exercise-induced myocardial ischemia in end stage renal disease patients with coronary artery disease (abstract and page 164, 3rd paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Airaghi and Wizemann to make the instant method of treating ischemia of the heart comprising administering alpha-MSH and EPO. The motivation and expected success is provided by both Airaghi and Wizemann. Airaghi *et al.* demonstrate that patients with acute myocardial infarction had plasma concentrations of alpha-MSH that were significantly greater than those in control subjects and propose that alpha-MSH would be useful in acute myocardial infarction. Wizemann *et al.* teach that erythropoietin reduces exercise-induced myocardial ischemia in dialysis patients with coronary artery disease.

Furthermore, it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method

and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and Ex parte Quadranti, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RMD
2/11/04

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